Early Check
Expanded health screening for your baby

Fragile X Premutation Fact Sheet for Health Professionals

North Carolina is conducting a pilot study to screen newborns for fragile X syndrome (FXS) with optional testing for fragile X Premutation

To gather additional information about the technical aspects of screening for FXS in newborns, the National Institutes of Health has awarded a contract to:

- RTI International
- University of North Carolina at Chapel Hill (UNC-CH)
- Duke University
- Wake Forest School of Medicine
- North Carolina State Laboratory of Public Health

This project team will perform laboratory testing and provide follow-up for infants who screen positive for Fragile X syndrome and Fragile X Premutation.

Fragile X Premutation

Fragile X Premutation (FXPM) is common in people of all ethnicities. Nearly 1 out of every 200 women and 1 out of every 400-500 men has FXPM. Most people with FXPM do not know they have it and do not notice any health effects.

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Effects of FXPM

The health effects of FXPM in a subset of adults is well established. The effects of FPXM on children's health and development is currently unclear, largely due to the lack of natural history data from largescale population studies.

In Children: Most children have no effects at all or mild effects of FXPM. Some children may have ADHD, social anxiety, and difficulties communicating and autism-like features. Early Check researchers are evaluating babies in a longitudinal study for early signs of these effects in babies and young children.

In Men: After age 50, approximately 40-50% of men with FXPM develop a progressive neurologic condition called *Fragile X-Associated Tremor/Ataxia Syndrome* (FXTAS), which causes tremor, ataxia, cognitive decline, and mood and personality changes, and is sometimes mis-diagnosed as Parkinsons. For more information about FXTAS, see the National Fragile X Foundation FXTAS

In Women: Approximately 20% women with Fragile X premutation have irregular periods, difficulty getting pregnant and can have menopause earlier than usual. This condition is called *Fragile X Premature Ovarian Insufficiency* (FXPOI). For more information, see the National Fragile X Foundation FXPOI Later in life, a smaller subset of women also develops FXTAS. This is usually milder for women than men. Some women with FXPM may experience anxiety and depression.

Cause

- Fragile X syndrome is caused by a mutation in the Fragile X gene, FMR1, which provides instructions for the Fragile X Mental Retardation Protein (FMRP) necessary for normal brain development. The FMR1 gene is on the long (q) arm of the X chromosome. The 5'-untranslated region of the gene is unstable due to the repetition of the trinucleotide cytosine-guanine-guanine (CGG).

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- The number of CGG repeats can expand when passed from mother to child, and a higher number of repeats results in greater chance of expansion. AGG interruptions can stabilize the gene and decrease the risk of expansion in some women.

- Most people have less than 45 CGG repeats, which is considered the normal range.

- 45-54 CGG repeats is called Gray Zone or Intermediate allele.

- Fragile X premutation ranges from 55-200 CGG repeats.

- When passed from mother to child, premutations can expand to greater than 200 CGG repeats, which is the full mutation. The full mutation results in hypermethylation of *FMR1*, leading to a decrease in the production of the fragile X mental retardation protein (FMRP) and causing the features associated with Fragile X syndrome.

Inheritance

- Premutations in boys can are inherited from the mother.
- Premutations in girls can be inherited from either parent.
- Because the number of CGG repeats expands when passed from mother to child, most children with FXS inherit the mutation from their mother, who has the premutation or less commonly the full mutation for fragile X syndrome.
- Women with FXPM can have children with the full mutation that causes Fragile X syndrome.

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Treatment in Children

The majority of children with FXPM are not expected to have health effects. For children with signs of developmental delay, early intervention services are recommended. Therapies and services should also be considered for children with evidence of psychiatric effects such as anxiety, ADHD, and maladaptive behavior.

Testing

Fragile X can be tested using a small sample of blood or saliva. Prenatal diagnosis and pre-implantation genetic testing are available and accurate.

- Parents of children with Fragile X syndrome (FXS) or Fragile X premutation (FXPM) should consider testing first to see if one of them also has FXPM.
- Testing should be considered for children, brothers, sisters, and more distant family members of people with FSX or FXPM, especially if they have problems with development, learning, or behavior.
- Fathers of women who have the Fragile X premutation should consider testing, especially if they have trembling hands, difficulty walking, or changes in personality or mood, or difficulty thinking.
- Family members who are pregnant or considering pregnancy should speak with their doctor or a genetic counselor to learn more about testing and options for planning a family.

More information

- **American Academy of Pediatrics Health Supervision Guidelines for Fragile X Syndrome**: http://pediatrics.aappublications.org/content/127/5/994
- **National Fragile X Foundation**: https://fragilex.org/
- **Early Check Fragile X Genetics Fact Sheet:** https://portal.earlycheck.org/en/fragile-x/genetics-of-fragile-x
- About **Early Check**: https://earlycheck.org

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